

REMARKS

Favorable reconsideration of the instant application in view of the present amendment and the following comments is respectfully requested. Claims 3-4, 12 and 15 are currently under examination in the application, and claims 3, 4 and 12 stand rejected while claim 15 is objected to. Upon entry of the amendment submitted herewith, claims 3 and 4 are amended and new claims 113 and 114 are added. Claims 113 and 114 are introduced as suggested by the Examiner in the Office Action at the bottom of page 3, to claim the subject matter encompassed prior to the present amendment by claim 15, by rewriting that claim in independent form including all of the limitations of the base claim and any intervening claims. Support for the above amendments can be found throughout the specification and claims as originally filed, including, for example, at page 1, line 28 through page 2, line 5; page 9, line 20 through page 10, line 1; page 25, lines 9-26; page 32, lines 10-24; and in Examples 1-4 (pages 81-89). No new matter has been added. The amendments and remarks herein should not be construed as acquiescence to the Examiner's stated grounds of rejection and are made without prejudice to prosecution of any subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

REJECTIONS UNDER 35 U.S.C. §102

Claims 3, 4 and 12 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Baker et al. (*J. Rheumatology* 16(1):7-14, 1989). The PTO asserts that the claims are drawn to methods of identifying agents involved in mitochondrial function comprising comparing ATP synthesis in biological samples comprising chondrocytes in the presence or absence of a candidate agent, and that Baker et al. disclose a method wherein ATP is measured in articular cartilage samples that contain chondrocytes, in the presence or absence of an agent (H₂O₂).

Applicants respectfully traverse these grounds for rejection. Further to entry of the amendment submitted herewith, the present invention is directed to a method for identifying an agent that alters mitochondrial function in a chondrocyte, comprising in pertinent part the step of comparing the rate of *mitochondrial* ATP synthesis in a biological sample that comprises a chondrocyte in the absence and presence of a candidate agent, or the step of comparing the rate

of *mitochondrial* ATP synthesis in a biological sample that comprises a chondrocyte obtained from a subject before and after administering to the subject a candidate agent.

According to the present invention, aerobic oxidative phosphorylation to generate ATP, an established *mitochondrial* function that was previously unrecognized in chondrocytes, is for the first time described and usefully exploited to provide the claimed agent-screening methods. As disclosed in the instant application and for reasons previously made of record in Applicants' submission on October 20, 2003 (in response to the Office Action of April 22, 2003), according to the claimed invention it is thus demonstrated that in articular chondrocytes *mitochondrial* function, and in particular aerobic *mitochondrial* oxidative phosphorylation, provides ATP that is required for extracellular matrix synthesis and PPi elaboration by these cells. (See, e.g., specification at page 25, lines 9-26; page 32, lines 10-24; pages 81-89.)

The prior art, exemplified by Baker et al., fails to disclose comparing the rate of *mitochondrial* ATP synthesis in a sample comprising a chondrocyte. Baker et al., in contrast to the present invention, fail to teach or in any way suggest a screening method that compares chondrocyte ATP synthesis described therein as the result of any process other than the *non-mitochondrial*, anaerobic respiration long held to account for glycolytic energy production in this cell type. Unlike the instant application, wherein can be found clear descriptions of methods for determining what portion of total intracellular ATP results from mitochondrial ATP synthesis (e.g., through the use of mitochondrial inhibitors, see pp. 81-89), Baker et al. thus fail to disclose or even contemplate methods for discriminating in chondrocytes between mitochondrially produced (i.e., aerobically generated) ATP and non-mitochondrial, glycolytically synthesized (i.e., anaerobic) ATP. Indeed, Baker et al. state that "articular cartilage depends largely upon glycolysis for its ATP biosynthetic capacity" (page 10, right column, eight lines from the bottom), and that in articular cartilage "metabolism is predominantly anaerobic" (page 13, right column, lines 1-5). Moreover, Baker et al. scrutinize G-3-PDH, a key enzyme in the glycolytic, *non-mitochondrial*, anaerobic ATP synthetic pathway (e.g., page 8, right column; pages 10-11, bridging paragraph) and conclude that decreased ATP levels detected in chondrocytes exposed to H₂O₂ are the result of impaired anaerobic (non-mitochondrial) respiration caused by peroxide-induced damage to G-3-PDH (page 13, right column, second paragraph). Nowhere, however, do Baker et al. disclose comparing chondrocyte *mitochondrial* ATP synthesis in the absence and presence of H₂O₂, the lone "agent" alleged by the PTO to be disclosed therein, and absent the

teachings of the present application the PTO fails to show that Baker et al. have necessarily compared mitochondrial ATP production in any assay.

It is axiomatic that for the PTO to establish a *prima facie* case of anticipation, each and every element of the claim must be present in a single prior art reference, which cannot be the case here because Baker et al. fail to provide a step comprising comparing the rate of *mitochondrial* ATP synthesis. The present invention is therefore readily distinguishable over the cited publication, such that the rejection under 35 U.S.C. §102 should be withdrawn.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The PTO rejects claim 3 under 35 U.S.C. §112, second paragraph, for indefiniteness. Specifically, the PTO asserts that essential steps are omitted, resulting in a logical disconnect between the recitation of the last clause in the body of the claim and the recitation of the preamble.

Applicants respectfully traverse this rejection and submit that the application satisfies all requirements of 35 U.S.C. §112, second paragraph. Nevertheless, and solely for purposes of advancing prosecution by making explicit what was implicit, upon entry into the record of the amendment submitted herewith, the final clause of the instant claim and the preamble are clear and consistent. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

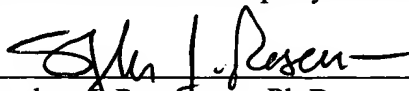
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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Enclosures:

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Petition for Extension of Time

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